Author: Susan Ellenberg
Title: Is the FDA in need of a major change in the way it regulates?

There have been many changes since the first Food and Drug Act was passed in 1906. In 1938, legislation established the requirement that drugs be proven safe prior to marketing. In 1962 the Kefauver-Harris Amendments to the Food and Drug Act, added the requirement that manufacturers prove that their drugs actually had the effect for which they would market it. This was a huge change, and resulted in an extensive review of all drugs marketed up to that time to determine whether they met the new requirements. Other major changes since then would include the 1976 Medical Device Amendments, setting new standards for the approval of medical devices and requirements for post-market safety surveillance; the accelerated approval regulations issued in 1991, permitting early approval on the basis of a less-than-definitive endpoint for which there was reasonable plausibility that effect on that endpoint would predict effect on the outcome of interest; and the Prescription Drug User Fee Act of 1992, which for the first time established deadlines for review of applications in exchange for user fees paid by companies submitting applications. Much legislation targeted at the FDA and the way it does business has been passed over the past 20-25 years, but for the most part these actions "established" pathways to regulatory action that already existed. For example, the FDA Modernization Act of 1997 stated that a single clinical trial with other supportive data might be sufficient to warrant marketing approval, but the FDA always had that authority and many drugs had been approved over the years on this basis.

The FDA's approach to innovative ideas about study design and analysis is undoubtedly cautious. It is certainly natural to be cautious about new approaches to the design and analysis of studies when you have the responsibility for the safety of the American public in your hands, but there is also the responsibility to take advantage of new approaches that could improve the efficiency of review while not increasing errors. That means that the FDA needs to be continually and actively assessing innovative approaches to its decision-making processes. The question of when a new approach is sufficiently well established to be the basis of the types of decisions the FDA has to make is "in the eyes of the beholder;" it is rare when a new design or analytical approach quickly becomes the standard (as happened in the early 1970s after Cox's paper (Cox, JRSS B, 1972) demonstrating an improved approach to survival analysis). A good example of the difficulties in determining the benefits and risks of a new approach is the area of surrogate endpoints. The FDA has approved drugs based on laboratory or physical measurement data for decades: antihypertensive drugs for lowering blood pressure, vaccines for establishing protective antibody levels, antiviral drugs for HIV that control the virus to below undetectable levels. In such cases, the connection between an effect on the surrogate and the expected effect on the clinical outcome are both highly plausible and have been confirmed (to the satisfaction of most) by extensive epidemiological studies and meta-analysis of clinical trials. But huge numbers of potential surrogate endpoints have been proposed but not accepted (yet) as a basis for regulatory approval. Case in point: the laboratory marker prostate specific

antigen (PSA) was touted for years as a measure that could serve as a clinical trial endpoint and regulatory approval, thereby speeding up drug development for treatment of prostate cancer. Many approaches to a PSA endpoint were advocated: simple change in PSA, PSA rise above a threshold, PSA velocity, changes in PSA velocity, etc.. There has been much debate within the community of urologic oncologists, and many analyses have been presented to support particular points of view. However, no consensus in the research community has been reached (Gomella et al, 2014); in fact, increased skepticism emerged about the validity of PSA measures as surrogates for recurrence of prostate cancer. The FDA's caution about using any PSA-based algorithm as a basis for drug approval (or accelerated approval) seems warranted.

A big problem with surrogates is that while they might predict the desired effect on the clinical outcome of interest, they typically provide no information about potential safety outcomes (Fleming and DeMets, Ann Int Med, 1996). For example, growing evidence about safety issues emerging with antidiabetic drugs approved on the basis of the surrogate measure HgA1C, have led the Agency to back away from reliance entirely on the surrogate and requiring substantial additional information on safety.
New approaches to study design and analysis are emerging all the time. FDA tends to be very open to innovative methods for early phase trials, as long as they do not perceive that the approach will put trial participants at unacceptable risk. Bayesian adaptive approaches and multi-stage designs are frequently used to make preliminary assessments of safety and efficacy; companies are relatively free to determine the approach they will take to determine whether to continue to develop an investigational product. When it comes time to conduct a Phase 3 trial to make definitive assessments of safety and efficacy, however, the FDA will strongly encourage approaches that are widely used in the scientific community and understood to yield valid results and protect against bias.

While there are, and always will be, ongoing debates about the optimal statistical approaches to design and analysis, and whether regulatory and funding agencies are too slow (or too fast) to adopt newer approaches advocated as improving efficiency and/or accuracy of findings, more serious challenges to the working of regulatory agencies have called for reversion to the time prior to the 1962 legislation that mandated demonstration of efficacy in addition to safety before a drug could be legally marketed. Such calls have been motivated by desire for access to potentially life-saving drugs at early stages of investigation, but also by a libertarian philosophy that decisions about one's health care should be subject to minimal restrictions and assumptions that freer use of medical products will ultimately lead to knowledge about the most effective approaches. This reactionary perspective on medical product regulation is extremely dangerous and short-sighted and would jeopardize continued gains in public health improvements.

Why dangerous? A medical product can cause benefit or harm—any agent with active ingredients will produce some effect. If there is no need to prove benefit, many products will be marketed that will cause only harm; most products in early stages of development are never shown to be effective (see for example U.S. Food and Drug

Administration 2017), but all these products could be marketed under the libertarian approach to regulation. It is folly to imagine that those causing serious harm would be identified quickly. Consider the case of antiarrhythmic drugs, proven to treat life-threatening arrhythmias effectively but that became widely used to prevent arrhythmias following myocardial infarction on the assumption that such use would save lives. But a randomized placebo-controlled trial showed that use of these drugs to prevent arrhythmias tripled the rate of sudden death (Echt et al, NEJM, 1991)! It is sobering to realize that an increase of this magnitude went unrecognized until a controlled trial was conducted. A similar but somewhat less dramatic example is that of hormone replacement in postmenopausal women, long thought to lessen the risk of cardiovascular outcomes but shown definitively in a randomized trial that such therapy actually increased this risk (Manson et al, NEJM 2003).

The clinical trials that demonstrated the harm caused by these products were not performed by industry; they were funded by the National Institutes of Health, which recognized the need to evaluate products being widely used for effects that were unproven. But if a plethora of new products floods the market, research agencies, foundations, and other groups that perform clinical trials, will be unable to take over the task of rigorously evaluating these products, tasks that should rightly fall to the commercial companies that will market and profit from them. The public will be faced with an increasing number of treatment options with no guidance as to which one(s) will actually work. Those affected will include individuals with life-threatening conditions who may now have access to a great many possible treatments with no data to help them choose the one most likely to help them.

Back in the 1980s and 1990s, the AIDS activists, who faced what was then an inevitably fatal disease with very limited treatment options, and who were extremely effective in getting public attention to their demands, advocated for expanded access programs to allow use of drugs with promising but preliminary evidence of safety and efficacy, and were instrumental in the development of the accelerated approval regulations that remain in place today. They stopped well short, however, of pushing for wide access to drugs based only on a limited amount of safety information. They recognized that what they needed were treatments that were proven to work—that a medicine cabinet full of drugs with no information about whether they would help or harm you was useless (Gonsalves and Zuckerman, BMJ 2015). They became strong advocates for rigorous trials that would give their community reliable guidance on therapeutic and prophylactic approaches for those infected with HIV. Other patient advocacy groups have taken similar stands. In the end, if serious challenges are mounted against our current system of medical product regulation, the loudest voices of protest may come from patients and their advocacy groups. They have the most to lose.

Author: Janet Wittes

Title: Is the FDA in need of a major change in the way it regulates?

"We actually believe in a strong, science-led FDA. We are a science-led organization that strives to hit high scientific standards and so we would expect the FDA to be well

staffed and focused also on those standards." – Pascal Soriot, Chief Executive of AstraZeneca

The FDA, like other regulatory bodies in other areas, straddles a knife edge between being too rigid and being too lenient. Decisions that regulators make preventing change (or, as anti-regulators would say, "obstructing change") can stifle innovation. On the other hand, over-permissiveness courts irreversible harm. As I write this, leaders of our US government speak in the voice of deniers of science. Regulators' failure to act can destroy our air, our rivers and streams, our oceans, the very way we live. If FDA regulators, who have in the last several decades based their judgments on science, begin to march to the drumbeat of anti-science, ineffective and even dangerous drugs and devices can enter the market. As the quotation from Soriot above exemplifies, responsible pharmaceutical manufacturers strongly support regulatory actions that reflect scientific data and judgment. Moreover, many patient advocacy groups have courageously defended the need for science in drug and device development. When we speak of "science", however, we must remember that no one - not investigators, not companies, and not regulators - have a monopoly on what characterizes good science.

Prior to 1962, the Food, Drug, and Cosmetic Act required drug companies to show that their drugs were "safe". But one cannot judge safety in the absence of data on efficacy. The Kefauver-Harris amendment of 1962 required that a drug also had to show substantial evidence of effectiveness for its intended use. Robert Temple of the FDA has pointed out, "That evidence had to consist of adequate and well-controlled studies, a revolutionary requirement."[i]As a consequence of that amendment and its "revolutionary requirement", the FDA began to regulate clinical studies in a more scientifically serious way. Since that time, the FDA has made major contributions to improving the design and conduct clinical trials which, in turn, has led to approval of safe and effective products and has prevented unsafe, ineffective products from entering the market. The same process that has led to rational decision-making in the past should be effective in this era of personalized medicine and new statistical methods.

Recently, populists have urged more direct advertising of drugs to the public. I hope that Congress moves instead to stricter regulation of this type of advertisement. The toxic combination of the public's lack of understanding of science coupled with Madison Avenue's skill at selling threatens public health. The cry for less immunization has led to increases in preventable communicable diseases[ii]; the public's insistence on antibiotics for viral infections has abetted the growth of resistant bacteria. Until we as a society are willing to spend the money on valid science education (don't hold your breath), regulators and a wide swath of the public should fight this push to expansion of direct advertising.

Of course, the FDA has made mistakes over the six decades since 1962. Some approved drugs and devices have turned out to cause harms too great for their benefits and, undoubtedly, some effective products have not been approved. Sometimes the FDA has been subject to strong political pressure to approve, or not to approve, specific products. Errors in both directions are inevitable in a system as complicated and large as the industry the FDA regulates. If the FDA continues with no change, I suspect we

will continue to see better drugs and devices enter the market. Moreover, the FDA has been thoughtfully struggling with assessing products post-approval; the Agency needs to continue, and even expand, its work in this area.

So my quick answer is “no” to the question of whether the FDA needs major change in the way it regulates. For the health of the public, the FDA still must base its judgments on approval from carefully performed controlled trials, usually randomized, that address important clinical questions in a way that allows rigorous evaluation of the product’s safety and efficacy. The FDA’s behavior over the course of these last 60 years has shown that it is not static; it has been open to innovation and improvement in design of studies and in their statistical analysis. Thus, if the FDA continues in its current path, the future is likely to see thoughtful, intelligent advances in methodology. In order to continue to do its job effectively, however, the FDA needs adequate staffing which, of course, means adequate funding. An overworked bureaucracy cannot be expected to drive innovation or even to keep abreast of innovation made outside its walls.

Assuming adequate funding, how can the FDA improve itself with the view towards more rapid decision-making but still maintain rigor? If one believes, as I do, that the basic structure is in place – a dedicated workforce that is eager to support bringing safe and effective products to market – radical change is not necessary and, in fact, is likely to be detrimental to the public health. Some small changes, however, can make big differences. The frustration many people (including me) often feel with the FDA stems not primarily from the Agency’s failure to innovate, but from more mundane problems related to process and, I contend, an apparent disregard of the needs and motivations of pharmaceutical and device companies. Below I give some examples – all come from actual cases but for reasons of confidentiality, I mask the diseases, drugs, and Divisions.

A major frustration experienced by those of us who work with or for drug and device companies comes from the fact that different Divisions seem to have dramatically different criteria for approval. I speak here not only of the differences between the Center for devices and the Centers for drugs and biologics, for those operate under different laws. I speak to Divisions within the same Center. Within the Center for Drugs, some Divisions approve drugs on the basis of outcomes that other Divisions would call surrogates.

Currently, acceptable statistical methods differ from Division to Division. What is important is whether the method makes sense in a particular case. Some Divisions or review teams appear to pay little attention to missing data – at least for continuous measures – or use methods many statisticians regard as inappropriate (e.g., last observation or baseline observation carried forward, LOCF or BOCF). A review of approvals in 2016 will show examples of continuous measures that simply ignored participants who did not have their final measurement (i.e., so-called “completers” analyses). Other Divisions will require methods that utilize techniques described in Little et al.[iii] [iv], a report commissioned by the FDA itself. It is not sensible, however, to compare the results of a trial that uses these more conservative methods to trials that have in the past used less rigorous ones. As science, including statistical methodology,

advances, the standards for approval must take the attendant changes into account. Otherwise, the bar for approval may become unattainable.

When the FDA has a set of questions that it sends to a company on a Friday afternoon with a requirement for an answer on Monday morning, or, worse, on the night before Thanksgiving expecting an answer the following Monday, or the day before Christmas with required answers by the end of the calendar year, the recipient companies understandably become frustrated and angry. Staff members must cancel their vacations; someone else has to do the cooking, etc. These and similar actions by FDA reviewers may satisfy the reviewers' assigned timelines, but the angst it brings to companies translates into negativity toward the FDA as whole.

Or consider the case of reviewing a Statistical Analysis Plan (SAP). FDA staff must understand that companies plan very carefully when databases will be locked and when the top line results will be ready (of course, the best laid plans often do go aft agley). Timing of the component processes is orchestrated carefully to satisfy investor needs and SEC requirements. To ensure meeting timelines, the programs must be ready to run as soon as the data are unlocked. The FDA tosses a monkey wrench into the process when it does not provide comments on the SAP for many months, and does not warn the company that a review is coming. If the comments arrive prior to database lock, all that is lost is money and time – which is bad enough. But if the comments arrive after the database lock and the statistical staff is already unblinded, the company finds itself in an untenable position. It cannot say it made changes to the SAP prior to unblinding; that is patently untrue. On the other hand, failure to "obey" the FDA is very risky. And now there is no time for dialogue between the company and the FDA.

So what should the FDA do to improve its relationship to developers and, ultimately, to speed the process of development and approval?

First, the FDA must maintain rigorous standards; that is, it must continue to set a high bar for approval. It must not succumb to the current arguments from the new administration and elsewhere that approvals should be based only on safety, not efficacy. Lack of rigor is not what responsible drug developers are asking for. "Having a high bar is a good thing… because it allows innovators to compete," says Len Schleifer, Chief Executive of Regeneron.

Second, increase the staff at the FDA. This may be a hard sell while the government is belt-tightening, but an overworked staff cannot perform maximally effectively. Our own staff tells our demanding clients that as statisticians we can produce work with two, but not three, of the qualities they want: speed, accuracy, and low cost. So it is with any group doing complicated work. If we, the US public, want the FDA to work quickly and to get the "right" answers, our society must give the Agency enough money to hire and maintain qualified staff.

Third, train the staff well so that they understand the issues involved in the project with which they are dealing and institute a careful process for reviewing reviews. This may require much more cross-Division discussion among entry-level reviewers, medical and statistical, than I suspect is happening. FDA staff needs to be conversant with the legal

standards applied to the science they are reviewing. Training means attending professional meetings – staff members should be encouraged to attend relevant meetings even when they are not presenting papers themselves.

Fourth, ensure that that staff appreciate the complexities of actually performing trials. Often an FDA review team imposes requirements that fly in the face of practicalities. The FDA should not assume that just because new graduates are up-to-date in science and methods they understand the context of a clinical trial, the typical standard of care in the disease under study, or the application of a method to a real problem. We as statisticians are often taught through “toy” examples that simplify the context of a problem in order to highlight a mathematical or statistical issue; real-life is cluttered with violations of simplicity.

Fifth, have the staff imbibe the maxim: “Your lack of planning is not my emergency”. The imbalance between the regulator and the regulated means that when the FDA imposes an unrealistic deadline (probably because of lack of planning or too small a staff), the company treats the request as an emergency demand. And that leads to lasting irritation with the FDA – not a good path for collaborative interaction.

These five steps are not revolutionary – they do not constitute an overhaul in the way the FDA is doing business. They are not easy to institute, but following them shorten the time to approval of drugs, increase the quality of discussion, and reduce the tension between regulator and those they regulate.

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[i] Robert Temple, quoted in http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/, viewed on February 12, 2017

[ii] Draper E. Report: Low vaccination rates in Colorado result in illnesses, costs. The Denver Post, Feb 7, 2015; updated ay 18, 2016..

[iii] Panel on Handling Missing Data in Clinical Trials (2010). The Prevention and Treatment of Missing Data in Clinical Trials. National Academies Press, 146pp.

[iv] Little, R. J., R. D'Agostino, et al. (2012). "The prevention and treatment of missing data in clinical trials." N Engl J Med 367(14): 1355-1360.

Author: Alex Tabarrok
Title: Is the FDA in need of a major change in the way it regulates?

The FDA is unprepared for the new world of personalized medicine. Consider what is possible now that nearly everyone carries with them the processing power of a 1990s Cray supercomputer. Smartphones equipped with sensors can monitor blood pressure, perform ECGs, even analyze DNA. Other devices being developed or available now include contact lens that can track glucose levels and eye pressure, real-time gait analysis, and head-bands that monitor and even adjust your brain waves.

The FDA has an inconsistent even schizophrenic attitude towards these new devices—some have been approved and yet at the same time the FDA has banned 23andMe and other direct to consumer genetic testing companies from offering some DNA tests because of "the risk that a test result may be used by a patient to self-manage". To be sure, the FDA and other agencies have a role in ensuring that a test does what it says it does (the Theranos debacle shows the utility of that oversight). But the FDA should not be limiting the information that patients may discover about their own bodies or the advice that may be given based on that information. Interference of this kind violates the first amendment and the long-standing doctrine that the FDA does not control the practice of medicine.

The world of personalized medicine has implications going beyond new devices and technologies. It also impacts how new drugs and devices must be evaluated. The more we look at people and diseases the more we learn that both are radically heterogeneous. In the past, patients have been classified and drugs prescribed according to a handful of phenomenological characteristics such as age and gender and occasionally race or ethnic background. Today, however, genetic testing and on-the-fly examination of RNA transcripts, proteins, antibodies and metabolites can provide a much more precise guide to the effect of pharmaceuticals in a person at a particular time. Drug targeting can reduce both adverse reactions and adverse non-reactions.

Targeting is beneficial but as Peter Huber has emphasized it means that drug development becomes much less a question of does this drug work for the average person and much more about can we identify in a large group of people the subset who will benefit from the drug? If we stick to standard methods that means every larger and more expensive clinical trials and more drug lag and drug loss. The FDA is already too conservative, as Andrew Lo, among others has shown. The FDA is conservative because when it approves a bad drug its error is visible but when it fails to approve good drugs the dead are buried in an invisible graveyard. The asymmetry of error visibility and the potential of personalized medicine both suggest that we allow for more liberal approval decisions. More liberal approval decisions will combine with improved techniques for monitoring individual patients to allow physicians to adjust prescribing in response to genetics and the body's reaction. Give physicians a larger armory and let them decide which weapon is best for the task.

Larger armories are also useful for a second problem. Many diseases are resistant to a silver bullet but succumb to silver bullets. The heterogeneity of patients, diseases and drugs and their multi-factorial combinations makes efficacy testing on final outcomes like mortality or life expectancy problematic. If we test three drugs against a disease each may fail to improve life expectancy even if all three drugs when used together or in sequence might cure the patient. But testing all possible combinations is far too costly to be reasonable. Combination therapies are best discovered in the field where knowledge can evolve and where individual circumstances of time and place can be adjusted for. The medical discovery process is why combination therapies and gold-standard treatments are often off-label treatments. Thus, we should be shifting our approval standards away from final-outcome mortality and towards safety and efficacy measured against the disease. Give physicians a larger armory and let them decide on tactics.

Philosophically I support a more libertarian approach to drug approval, one that offers greater respect for patient autonomy. I have deemed this a Consumer Reports model of the FDA. Consumer Reports evaluates products and gives recommendations but it doesn't forbid consumers from making choices given their own values and constraints. Consumer Reports helps consumers to make better choices. Similarly, a less paternalistic FDA would provide more information to patients and doctors, but it would also leave more choices in their hands. In addition to offering greater respect for patient autonomy, I believe that such an approach would lower costs and increase the number of new drugs and devices offering tremendous value to patients in the United States and the world.

Author: Geert Molenberghs
Title: Is the FDA in need of a major change in the way it regulates?

It is important for a regulator to carefully balance sometimes conflicting concerns: protecting the public; ensuring that drug and devices development remains viable, also economically; keeping up with scientific developments and breakthroughs, emerging new methods, and changing insight.

While it is necessary beyond question to have crystal clear procedures in place, this does not mean that every aspect of the regulatory framework should be time invariant. For example, when in one of the relatively early phase of the AIDS epidemic co-enrolment appeared on stage, partly forced by patients' rights group, and against what regulators, academic researchers, and industry considered wise, it turned out to be a very beneficial device. While co-enrolment challenged an until then seemingly foundational aspect of a clinical trial used for drug approval, and while it raised a number of complex methodological issues, it is partly to be credited for the development of highly active anti-retrovirus therapies.

What is needed is clear mechanisms to continually examine the need for change and then procedures to implement such change. If rules are conceived 'for eternity,' the consequence is that no agreed upon mechanisms would exist regarding change. It is an illusion though that change can be kept out of the door and thus, when it inevitable happens, adjustments and changes would be governed by *ad hoc* procedures – precisely the reverse of what is intended. In other words, change and evolution should be 'domesticated.'

Evidently, this cannot be done within the regulators' community alone, but should rather be done in concertation with the research communities in industry and academia, as well as with other stakeholders, in particular patients, payers, etc.

It is fair to say that change happens all the time, and over recent decades regulators worldwide have contributed to structures that feel the pulse of changing evolutions and new developments. For example, joint conferences, *ad hoc* and on a regular basis,

between regulators, academia, and industry are being held to the benefit of furthering insight. I would like to refer to workshops involving FDA and industry, EMA (European Medicines Agency) and the Drug Information Association (DIA), etc. Some of these are organized in conjunction with further partners such as the American Statistical Association (ASA), the Society for Clinical Trials (SCT), the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI), etc.

Another important vehicle is working parties and hearings on particular topics. I will mention a few.

The FDA commissioned a project, under the auspices of the National Research Council and headed by Rod Little, that led to the 2010 report on *Prevention and Treatment of Missing Data in Clinical Trials.* Working party members held current and past positions in all three sectors (academia, industry, regulatory). Also, they came from various backgrounds within statistics and clinical trials (for example, some are experts in survey sampling, allowing for fruitful cross-sub-discipline symbiosis). Representatives from different and sometimes competing schools of thought partook. While the FDA took the initiative and, at properly organized points in time during the process they could state their expectations and feedback could be exchanged, the working party was entirely independent.

The EMA has organized hearings on such topics as subgroup analysis. This allows input from the broader research communities, stakeholders in the topic and in different but related topics (e.g., orphan diseases), industry, and fellow regulators.

A structure not yet mentioned but extremely important is the International Conference on Harmonization (ICH). A large majority of the issues of importance to a regulatory body are not confined to that body alone, but is of international significance. An example is the recent revision of the ICH-E9 on the statistical principles for clinical trials, where regulators and other stakeholders from the US, Europe and Japan have collaborated.

A related international initiative is the recent working group on the concept of estimands. It is a simple but sometimes forgotten truth that discussing estimators, procedures, etc. is rather pointless if one has not reflected on what is being estimated. It is therefore a

crucial endeavor to clearly define concepts and language, and assess how this can enhance drug development and the practice of clinical trials. A successful outcome of this project will be transforming in a number of areas. To give one example, sensitivity analysis regarding missing data can be harnessed better so that, routinely, a sensitivity analysis will encompass different estimators, under differing assumptions, but for the same estimands.

Evidently, many scientific evolutions that are taking place right now and undoubtedly will in the future, will make the need for initiatives like the ones described above more needed than ever. Some evolutions are broad and general, such as big data and data science. Without engaging here in a discussion as to what they now really mean, it is important to assess sooner rather than later what the implications are for drug development, for the regulatory framework, and for the regulators.

Other evolutions are more directly relevant for medicine, clinical practice, and hence for regulators. A key example is personalized medicine. I think it is a nice example to underscore just how much collaboration is needed. While scientific research is not the exclusive right of academic and other research institutions, it seems fair to say that there are important and highly technical research efforts needed, that go beyond what regulators and industry want to allocate their resources to. At the same time, there is a risk, when research is solely done in an academic environment, that 'mathematization' goes in the direction of ever more abstract and ever more general frameworks, that somewhat lose attraction to and relevance for biopharmaceutical development. Hence, joint projects, ideally co-sponsored between granting bodies, industry, and/or regulators, should be given a prominent place.

So, all in all, it seems that a good number of initiatives have been taken in the past, to ensure modernization of thinking and embracing of emerging concepts and tools. However, many of these are still of an *ad hoc* nature. It appears important to structurally organize the consultation and learning processes as much as possible, while indeed leaving room for spontaneous initiatives as well. On a regular basis, and following a clear but flexible protocol, it would seem important to identify areas where development and consultation is needed. Following this, there should be procedures to then identify to best achieve a particular goal, where a number of choices need to be considered. Without being complete, these would include:

- Regulators to involve: FDA, EMA, Japan, ICH, others,…
- Other stakeholders to involve:
    - Academia and research institutions (if so, what disciplines)
    - Industry
    - Patients
    - Payers, insurance companies,…
    - …
- Funding (internal funding, external resources, funding agencies, etc.)

In conclusion, regulators should regulate how their own organization learns and transforms, in an orderly and stable fashion, easy to audit and very transparent, and in concertation with all relevant stakeholders, whilst at the same time strictly maintaining its independence. The latter means that the ultimate decision to change a procedure or adopt a new one, is strictly with the regulator, and with the regulator only.

A key requirement is that agencies like the F.D.A. should be scientifically strong and independent, with a clearly defined mission and shielded from overly strong political and economic influences. In spite of their long standing, they may be too vulnerable at this time. Clear checks and balances in this respect are crucial.

Author: Andrew Lo

Title: New Directions for the FDA in the 21st Century

The Food and Drug Administration is a remarkable agency, one of the crown jewels of the U.S. government. Its staff and structure are dedicated to safeguarding American public health, and although we sometimes complain about its role as gatekeeper, we all sleep better knowing that our foods and drugs have passed the FDA's careful scrutiny. Its regulatory scope and process reflects the technical demands of its responsibilities, and the FDA is one of the very few federal agencies that have taken a lead in defining and developing the new field of regulatory science.[1]

Although no regulator can or should attempt to anticipate every innovation that might require new approaches to regulation, in the case of healthcare, there are three areas of opportunity that may call for equally innovative responses from the FDA. The first is in making more use of predictive analytics to inform the FDA's deliberations. As the trusted third party charged with the mandate to review clinical evidence for all drugs and devices marketed in the U.S., the FDA is privy to enormous amounts of valuable data. More aggressive rates of data collection will require more investment in data science, but this is only appropriate since such data is paid for with the flesh and blood of courageous patients enrolled in clinical trials. The array of potential new therapies today is dizzying, in immune-oncology, gene therapies, and the growing number of applications of gene editing. To meet this torrent of potential new applications, the FDA will need to expand its information technology base, not only to include new forms of data, but also to integrate its earlier collections of clinical trial information.

Recent advances in data science using machine-learning techniques such as support vector machines and deep learning networks have transformed several other data-intensive industries such as consumer credit provision, insurance, marketing, and online retail sales. Given the magnitude and scope of data entrusted to the FDA, a host of insights regarding the viability of certain therapeutic lines of development should be available if the right estimation methods are used. These insights can lead to better decisions in the approval process, and can also allow the FDA to provide more refined guidance to the industry regarding unmet needs, overcrowding in certain therapeutic domains, and factors most predictive of clinical success and failure. The Information Exchange and Data Transformation (INFORMED) initiative in the FDA's Office of Hematology and Oncology Projects[2] may be just the beginning of a broader effort to bring data science to the agency.

The second area of opportunity for the FDA is in information sharing. While it would be a violation of trust for the FDA to release any of its data into the public domain, there may be a middle ground in allowing certain aggregated information to be shared so as to benefit the public good. For example, more accurate estimates of the probabilities of success of clinical trials by indication could lead to more efficient allocation of scarce resources, and such estimates are unlikely to jeopardize the proprietary information of any single industry sponsor. New methods developed by computer scientists for sharing selective portions of data—known as secure multiparty computation—may be particularly relevant for improving knowledge sharing while preserving privacy and protecting intellectual property. INFORMED may be an ideal testbed to evaluate the feasibility and desirability of such algorithms for the biopharma industry.

The third and most important opportunity for the FDA to explore is to develop a framework for reflecting the patient perspective in its deliberations. Section 3002 of the recently passed 21st Century Cures Act requires the FDA to develop guidelines for patient-focused drug development, which includes collecting patient preference and experience data and incorporating this information in the drug approval process. This is particularly relevant in cases where the FDA is asked to review candidate therapies for terminal illnesses that have no existing treatments. In response to these urgent cases, the FDA has implemented several programs to expedite the approval process.[3] And in situations where the clinical evidence of efficacy is overwhelming, the FDA can move extremely quickly. For example, in the case of imatinib (Gleevec), which showed remarkable efficacy in Phase 1 for treating patients with chronic myeloid leukemia, the drug application was reviewed in a mere two and a half months, and went from Phase 1 to FDA approval in two and a half years under the FDA's Accelerated Approval process.[4] However, for less clear-cut cases—which comprises the vast majority of candidate therapies—the approval process is not nearly as quick, and even a Fast Track review may lack the sense of urgency that a terminal patient experiences. Moreover, none of the FDA's programs systematically measure and incorporate patient preferences explicitly in the approval decision, nor do any of these programs call for changing the statistical threshold by which clinical trials are evaluated.

In several recent studies, my co-authors and I propose a formal framework for reflecting patient preferences in the FDA's approval process using a well-known technique called Bayesian decision analysis (BDA). Briefly, BDA begins with the recognition that two types of errors are possible in deciding whether to approve or reject a new therapy: rejecting an effective therapy (a false negative) and approving an ineffective therapy (a false positive). The traditional approach for managing these errors is by setting a statistical threshold of 2.5% for the likelihood of a false positive, so that only those therapies exhibiting effects exceeding this stringent threshold in clinical trials will be approved.

In statistical jargon, these are therapies with "*p*-values" lower than 2.5%. BDA takes a different approach: instead of using the same threshold of 2.5% for all cases, it allows us to compute an alternative threshold that minimizes the expected harm to current and future patients due to the two types of errors. For example, in desperate situations like pancreatic cancer or glioblastoma where death is imminent and no effective treatments exist, patients may be willing to face a greater than 2.5% chance that a drug is ineffective given their alternative. BDA offers a method for computing the approval threshold that minimizes the average harm to current and future patients from false positives and negatives, where harm includes patient-focused input such as quality-adjusted life years lost. In the case of glioblastoma, our application of BDA yields an optimal threshold of 47.5%, a much less restrictive approval threshold that is likely to increase the number of drugs for this terrible disease.[5]

A natural consequence of this laxer threshold is, of course, more false positives—and the potential for a greater number of patients with adverse side-effects. This can be addressed through more vigilant post-approval surveillance by the FDA, and greater requirements for drug and device companies to provide data to the FDA on patient experience following approval. Failure to provide such data or evidence of an ineffective therapy can be grounds for revoking the approval.

However, past experience shows that revoking an approved drug is extremely challenging for several reasons. Therefore, implementing BDA may require legislation to create an entirely new program for "Speculative Therapies" at the FDA. Such a program might involve provisional approval of a candidate therapy consisting of a two-year license to market the therapy to a pre-

specified patient population, no off-label use of the therapy, and regular monitoring and data reporting to the FDA by the manufacturer and/or patients' physicians during the licensing. At the end of the two-year period one of three outcomes would occur: (a) the manufacturer can apply for a second two-year license (only one renewal will be allowed); (b) the license expires; or (c) the therapy receives the traditional FDA approval designation. Of course, at any point during the two-year period, the FDA can terminate the license if the accumulated data suggests an ineffective or unsafe therapy. While such a process may impose greater burdens on patients, manufacturers, and the FDA, it may be worthwhile if it brings some relief to patients facing mortal illnesses and extreme suffering. In this respect, a Speculative Therapies program may be viewed as a middle ground between a standard clinical trial and an approval, similar in spirit to the adaptive designs of sophisticated clinical trials with master protocols such as I-SPY 2,[6] LUNG-MAP,[7] and GBM-AGILE,[8] in which patient care and clinical investigations are simultaneously accomplished.

Of course, in practice the FDA considers many factors beyond *p*-values in making their decisions. However, that process is opaque even to industry insiders, and the role of patient preferences is unclear. The recent FDA approval of the Duchenne muscular dystrophy drug eteplirsen (Exondys 51) despite relatively weak clinical evidence suggests that the FDA does take the patient's perspective into account. BDA provides a systematic, objective, adaptive, and repeatable framework for explicitly incorporating patient preferences and burden-of-disease data in the therapeutic approval process. As the noted biostatistician Don Berry said, "We should also focus on patient values, not just *p*-values."[9]

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Author: Tom Flemming, David DeMets, Lisa McShane
Title: The Role, Position and Function of the FDA - The Past, Present and Future

The health of the nation and the world has been profoundly positively influenced by the pursuit and implementation of evidence based approaches for the prevention and treatment of diseases. The U.S. Food and Drug Administration (FDA), along with other regulatory authorities throughout the world, have made critically important contributions to this pursuit. The FDA recognizes their mission is to be "*responsible for protecting public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation…FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.*"

The FDA has effectively addressed their mission by providing consistently strong leadership and oversight that has been of integral importance to protecting public health. The FDA has been highly influential in the attainment of substantial evidence of efficacy and safety of approved drugs, biologics and devices by ensuring achievement of proper standards for design, conduct and analysis of registrational trials. Among these significant favorable influences have been:

~ Encouraging stepwise clinical development;

~ Having proper controls in registrational trials, often best achieved through use of randomization;

~ Properly addressing multiplicity through pre-specification of primary and secondary outcome measures and primary methods of analysis;

~ Recognizing reliability and interpretability of efficacy is enhanced by assessing effects on direct measures of how a subject 'feels, functions or survives,' and recognizing the likelihood

of being misled when relying on replacement endpoints such as biomarkers that have simply been shown to be correlated with direct measures of tangible benefit and often do not capture risks adequately;

~ Recognizing the value of blinding when outcome measures are subjective;

~ Guiding proper designs of non-inferiority trials;

~ Ensuring clinical trials are designed and conducted in a manner to assure the safety and ethical protection of study participants

~ Enhancing the quality of trial conduct by encouraging timely enrollment, best real world achievable adherence to experimental and control regimens, pro-active efforts to maximize retention, and maintaining confidentiality of efficacy data in ongoing trials;

~ Recognizing that exploratory analyses usually should be viewed as generating hypotheses; and

~ Recognizing the need for confirmatory trials, especially in settings where positive predictive probabilities for efficacy are not strong (such as when obtaining marginally positive results in a setting where the pre-trial likelihood of meaningful benefit was rather low), or when post-hoc analyses would properly be viewed as being hypothesis generating, or when important safety signals have been identified.

The FDA's role is of integral importance in addressing conflicts of interest in medical research. There is a pervasive interest in obtaining positive results that would enable increased options for caregivers to offer their patients, and would provide enhanced reputations for researchers and financial benefits to sponsors. While these are valid interests, they can conflict

with the greater interest in ensuring the integrity and reliability of clinical research. There is an inherent high level of multiplicity in clinical research, arising from multiple outcome measures, methods of analysis, subgroups of patients and analyses over time. Without proper oversight including that consistently provided by FDA, such multiplicity provides strong risks for misleading conclusions, especially when data are explored by those looking for positive results [1]. This was discussed in a presentation in May 2016 by commentator John Oliver in 'Last Week Tonight' [2], who recognized such risk for bias "*because of scientists feeling pressured to come up with eye-catching positive results…to get those results, there are all sorts of ways that, consciously or not, you can tweak your study, you can alter how long it lasts, our make your random sample too small to be reliable, or engage in something that scientists call P-Hacking…it basically means collecting lots of variables and then playing with your data until you find something that counts as statistically significant but is probably meaningless.*" These issues are of particular concern in the pursuit of personalized medicine due to the inherently high magnitude of multiplicity in identification of subgroups of patients who benefit from new therapies, the need for accurate clinical laboratory tests to appropriately guide personalized medicine strategies, and the still evolving regulatory oversight process for laboratory tests. Negative consequences of poorly understood or weakly applied regulatory oversight processes for laboratory developed tests have been vividly demonstrated. There are numerous examples of clinical tests promoted for personalized medicine that were made clinically available prematurely [3] or that were incorporated into clinical trials where they were used to guide treatment decisions but later found to be based on flawed evidence or even fraudulent data [4]. Failure to insist on good clinical and laboratory practices, apply rigorous standards for the design, conduct, and analysis of biomedical research, and implement safeguards to address conflicts of interest poses

threats to the integrity of biomedical research and exposes patients to potential harms.

The FDA's ability to address its responsibility *"for advancing the public health by helping to speed innovations"* is enhanced by its privileged position of having broad access to ongoing clinical research. The efficiency of the scientific process is increased if we are enlightened by the lessons learned from past experiences, whether they be successes or failures. However, for pharmaceutical and biotech companies that collectively lead a substantive component of the clinical research effort to develop and evaluate drugs, biologics and devices, clear competitive advantages are achieved by protecting their confidential and proprietary information and trade secrets. This provides strong motivation for these companies to reveal as little as possible about the successes and failures in their scientific process. Fortunately, regulatory authorities have broad access to sponsor's data through their oversight responsibilities. These broad experiences enable FDA to be more enlightened when they guide clinical trial development and to make more informed judgments about whether evidence is sufficient for marketing approval and about how to proceed when it is not.

Reducing FDA's regulatory authority, for example by substantially lowering the standards for strength of evidence required for marketing approval, and in turn increasing the reliance on post-marketing observational studies to provide enlightenment about efficacy and safety, likely would be treacherous for the public. Interventions often have meaningful positive or negative effects on the rate of key efficacy or safety outcomes. When these effects are not at least 5- to 10-fold in magnitude, there is considerable risk that they would not be detected through evidence from the marketplace that lacks formal controls. For illustration, hundreds of thousands of patients received encainide and flecainide for arrhythmia suppression after myocardial infarction, until the randomized Cardiac Arrhythmia Suppression Trial established

such use actually tripled the death rate; hormonal replacement treatment was widely used by menopausal women, until the randomized Women's Health Initiative trial established such use increased the risks of heart attacks and strokes; Cox-2 Inhibitors, Vioxx and Bextra, were widely used for pain relief in osteoarthritis and rheumatoid arthritis patients until randomized clinical trials collectively involving fifty thousand patients revealed these agents increased the risks of MACE, (i.e., cardiovascular death, stroke or myocardial infarction); and Beta-Carotene was widely used until the randomized Beta-Carotene and Retinol Efficacy Trial revealed such use induced increased incidence and risk of death from lung cancer. Numerous other examples reveal peril that would result from a regulatory strategy heavily dependent on evidence from the marketplace.

We will continue to hear arguments about the merits of weakening regulatory standards. While doing so surely could reduce costs of drug development prior to regulatory approval, such an approach could induce far greater costs to the public and even to drug developers.

For the public, there would be important opportunity costs, occurring when patients chase some novel intervention having evidence that is more hype than substance: these patients may be giving up other options that would have provided benefit. Furthermore, allowing widespread expenditures on interventions for which there is only scant evidence of true benefit and safety would further accelerate the rate of increase in costs of health care and, given that resources available for health care are not unlimited, would adversely impact the level of resources available for safe and effective interventions.

For drug developers, there could be increased risks from litigation due to safety events either that are real but were not discovered by the less rigorous regulatory process, or that are

only alleged to be related to a product but where its sponsor does not have the scientific evidence to justify its safety.

Weakening FDA's regulatory standards in order to reduce the burden of the drug development process could fail to achieve the intended outcome since reliable scientific evidence about the efficacy and safety of drugs, biologics and devices, usually best provided by controlled clinical trials that are properly designed, conducted and analyzed, is of critical importance not to only to the FDA, but also to other regulatory authorities throughout the world and surely to patients, payers and providers who face the complex challenges of choosing among available health care options.

It might be argued that stronger rather than weaker regulatory standards are needed. Evidence is provided by Liz Szabo's article, appearing in USA Today on February 9, 2017,[5] entitled "*Treating Cancer: Hope vs Hype Dozens of New Cancer Drugs Do Little to Improve Survival, Frustrating Patients*". Concerns are reported "*that the Food and Drug Administration is approving cancer drugs without proof that they cure patients or help them live longer*", and that more cancer drugs are being approved simply based on effects on the biomarker-based endpoint, 'progression free survival'. Vinay Prasad of Oregon Health and Sciences University provided evidence that the link between effects on 'progression free survival' and effects on overall survival often is weak. FDA's Richard Pazdur conveyed the proper intention, "*FDA wants to give patients a chance to benefit as soon as possible,*" at times relying on long term post marketing studies to provide the evidence needed to reliably establish efficacy and safety. Researcher Diana Zuckerman of the National Center for Health Research reported that many of these post marketing studies have not provided clear evidence, with Prasad recognizing it is uncommon for post marketing studies to be completed establishing survival advantages when

drugs are approved without such evidence. Otis Brawley, chief medical officer at the American Cancer Society, expressed concerns that FDA is lowering its standards, and that "*Studies suggest that both patients and doctors tend to overestimate drugs' benefit, but underestimate their risks and side effects*." This access has come at significant financial cost. Referencing the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, the article reports that "*Cancer drugs approved last year cost an average of $171,000 a year."*

Is the FDA in need of a major change in the way it regulates? While the FDA has been very effective in addressing its mission, nevertheless as with any successful entity, it will be important to pursue thoughtful and creative approaches, in order to adapt to the changing landscape of medical product development and enhance the ability of the FDA to protect public health in the future. The following should be among such approaches:

- Enhance the FDA's ability to address their mission by ensuring they have necessary resources and by reducing the influence of political or special interests that conflict with their primary goals of protecting the public.

- Encourage ongoing consideration of creative approaches to the scientific process and to regulatory oversight that would improve the efficiency while maintaining or increasing reliability, and that would effectively address new types of challenges that may emerge. Some potential approaches include:

  - Increase support for pragmatic trials, conducted in real world settings with streamlined procedures for screening and enrollment, with endpoints (such as mortality in oncology trials) that are highly relevant to subjects and that can be readily assessed in a straightforward manner, with reduced burdens to subjects and researchers and with reduced risk of missing data that

would compromise the ability to obtain unbiased assessments of treatment benefits and risks.

- Reduce the cost of clinical trials by reducing the collection of information that is not of integral importance to the benefit-to-risk assessment and, in particular, reduce line-by-line on site monitoring of data collection forms (efforts related to those of the previous FDA Commissioner, Robert Califf [6]).

- Pursue creative approaches to achieve timely and reliable evaluation of personalized medicine interventions, recognizing the importance of identifying outcomes having sufficient sensitivity that intervention effects can be addressed in smaller sample sizes, recognizing reliability is greatly enhanced by having randomized controls and using direct 'feels, functions, survives' outcome measures, and recognizing the importance of increasing the number of participating clinical sites and expanding their geographic reach and accessibility.

- Continue use of regulatory approaches for providing early public access, such as accelerated approval, while improving the ability to achieve timely completion of validation trials that reliability address effects on 'feels, functions, or survives' outcome measures, such as by use of pragmatic trials conducted in a large number of sites, and improving the ability to withdraw marketing approval when validation trials do not provide evidence in a timely manner that reliably establishes substantial evidence of efficacy and safety.

- More strongly encourage that data from completed randomized clinical trials be shared in a timely manner to enhance transparency and enlightenment, as advocated by the Institute of Medicine.

- Increase the collaboration between regulatory authorities worldwide; this is particularly important when addressing emerging public health emergencies.

If we continue to maintain regulations in areas other than health care, such as authorizations required to drive a motorized vehicle including having a driver's license, abiding by laws regarding use of seat belts and helmets, and carrying insurance, then surely there is need for proper regulatory oversight of the health care process. Public health is enhanced by evidence based medicine, where the interests of the public are protected by the oversight of the research process provided by regulatory authorities such as FDA. The goal is not simply to ensure availability of interventions for the treatment and prevention of diseases to enable to public to have 'choices', but rather to ensure there are adequate insights about benefits and risks of these interventions to enable 'informed choices'. Attainment of the best possible outcomes for patients will require careful balancing of benefits and risks for the full spectrum of medical products [7]. A strong FDA has an integral role in achieving that goal.

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